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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/970,088	10/02/2001	Edwin C. Gravereaux	71417/55062	9526

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EXAMINER	
KAPUST, RACHEL B	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 05/20/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/970,088	GRAVEREAUX ET AL.	
	Examiner	Art Unit	
	Rachel B. Kapust	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-46* is/are pending in the application.

4a) Of the above claim(s) *10-21 and 31-41* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-9, 22-30, and 42-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 October 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I (encompassing claims 1-9, 22-30, and new claims 42-46) is acknowledged. The traversal is on the ground(s) that there is not a substantial burden on the Examiner because searches for all of the groups would overlap significantly.

Applicant's arguments have been fully considered but have not been found to be persuasive. Regarding Applicant's argument that there is not a substantial search burden on the Examiner, as stated in the office action of paper no. 1203, the different groups of methods, pharmaceutical products, animal models, polynucleotides, and polypeptides require different, non-contiguous searches, as evidenced by their different classification. They require separate searches of separate databases. A search for nucleotide sequences that encode a protein yields no comparison of that protein to other proteins; such comparison requires a separate search that yields no comparison of one polynucleotide sequence to another. A search for a pharmaceutical product comprising VEGF-2 would not overlap with a search for VEGFR-3 polypeptides. A search for an animal model for identifying compounds that reduce lymphedema is separate from a search for VEGF or VEGFR-3 because the model is used for screening any compound and additional considerations are required. The search for methods of use is separate because it requires additional considerations as to the methodology itself. Thus to consider all of these groups would constitute an undue burden because each requires considerations that are separate from each of the others.

The restriction requirement is still deemed proper and is therefore made FINAL. Claims 10-21 and 31-41 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention. Claims 1-9, 22-30, and 42-46 are under consideration.

Priority

An application claiming the benefits of a provisional application under 35 U.S.C. 119(e) should not be called a "continuation" of the provisional application since an application that claims benefit of a provisional application is a nonprovisional application of a provisional application, not a continuation, division, or continuation-in-part of the provisional application. See MPEP 201.07 [R-1]. Thus, the specification should be amended so that it reads "The present application claims priority from U.S. Provisional Application No. 60/237,171 filed on October 2, 2000".

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code (see. p. 18). Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

The use of the trademarks CIS-SULFUR COLLOID™ (p. 33), ULTRA-TECHNEKOW™ (p. 33), MILLEX™ (p. 33), GENESYS™ (p. 34), READY GELS™ (p. 37), HYBOND™ (p. 37), HYPERFILM™ (p. 37), IMMUNOPURE™ (p. 37), SUPERSCRIPT II™ (p. 38), PBLUESCRIPT™ (p. 38 and 39), and EAGLESIGHT™ (p. 39) have been noted in this application. They should be capitalized wherever they appear and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Objections

Claim 4 is objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim should refer to other claims in the alternative only. See MPEP § 608.01(n).

Claim 6 is objected to because of the following informalities: there is a typographical error in claim 6. Claim 6 reads "wherein the increase in new lymphatic vessel grow is at least about" and it should read as "wherein the increase in new lymphatic vessel growth is at least about". Appropriate correction is required.

Claim 29 is objected to because of the following informalities: there is a typographical error in claim 29. Claim 29 reads "the methods of claim 1" and it should read as "the method of claim 1". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-9, 22-30, and 42-46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inducing formation of new lymphatic vessels in a mammal by administering VEGF, does not reasonably provide enablement for a method of inducing formation of new lymphatic vessels by administering fragments of VEGF. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention; 2) state of the prior art; 3) relative skill of those in the art; 4) level of predictability in the art; 5) existence of working examples; 6) breadth of claims; 7) amount of direction or guidance by the inventor; and 8) quantity of experimentation needed to make and/or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims are drawn to methods for inducing the formation of new lymphatic vessels by administering fragments of VEGF. However, Applicants have provided no guidance as to what

size fragment would be sufficient or what region of VEGF would be sufficient for achieving the formation of new lymphatic vessels. Applicants define an "effective fragment" as an "amino acid sequence that exhibits at least about 70%, preferably at least about 80% to about 95% of the lymph vessel promoting activity of the corresponding full-length protein" (see p. 17, lines 1-4 of the specification). Certain positions in a protein sequence are critical to the protein's structure/function relationship, such as various sites or regions directly involved in binding, activity, and in providing the correct three-dimensional spatial orientation of binding and active sites. One of skill in the art would not know which amino acids may be deleted from VEGF in order to yield effective fragments of VEGF. VEGF itself is alternatively spliced into at least five variants which give rise to peptides comprising 121, 145, 165, 189, and 206 amino acids. Zhang et al. teach that VEGF121 is more angiogenic and tumorigenic then the 165 and 189 isoforms (Zhang et al. (2000), *British Journal of Cancer* 83(1): 63-68). Thus, depending on the amino acid sequence of the protein, variations may occur in the activity of VEGF.

Due to the large quantity of experimentation necessary to generate the fragments recited in the claims and screen the same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on polypeptide structure and function, and the breadth of the claims which fail to recite any structural limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

Claims 1-9, 22-30, and 42-46 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims are drawn to a genus, *i.e.* a method of inducing formation of new lymphatic vessels by administering VEGF. The genus includes methods of inducing formation of new lymphatic vessels by administering fragments of VEGF. Applicants have disclosed one species, a method of administering VEGF, but have not disclosed sufficient

species for the broad genus which includes administering any fragment of VEGF to induce formation of lymphatic vessels.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, and any combination thereof. The instant disclosure of a single species of protein, VEGF, does not adequately describe the scope of the claimed genus, which encompasses hundreds of different peptides with varying structures and functions. The instant specification fails to provide sufficient descriptive information, such as regions of VEGF which are critical to inducing formation of lymphatic vessels. Applicants are claiming a species which has not been sufficiently described, *i.e.* Applicants are claiming sequences of VEGF that have not yet been identified. Only once the VEGF fragments have been generated and their functions have been determine can a person of skill in the art determine that the VEGF fragments are able to induce formation of lymphatic vessels. Thus, no identifying characteristics or properties of the instant VEGF fragments are provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed. Accordingly, one of skill in the art would doubt that Applicants had possession of the claimed species at the time the application was filed.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed nucleic acid molecules, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required.

See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, the disclosure of VEGF is insufficient to describe the genus. Therefore, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe and enable the genus as broadly claimed.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-3, 5-8, 26, 29-30, and 45-46 are rejected under 35 U.S.C. 102(e) as being anticipated by Achen *et al.* (U.S. Patent Application Publication 2002/0127222). Claims 1-3, 5-8, 22, 25, 26, 29-30, and 45-46 are drawn to methods for inducing formation of new lymphatic vessels in mammals by administering effective amounts of VEGF or effective fragments thereof sufficient to form new vessels in mammals. The VEGF may be sufficient to increase growth of new lymphatic vessels following lymphedema. The mammal being treated may be a rabbit, rodent or primate or more specifically a human patient. Achen *et al.* teach administering VEGF-D or effective fragments thereof to patients to stimulate lymphangiogenesis for the treatment or

alleviation of lymphedema (see paragraph 0044 and claim 42). Thus, claims 1-3, 5-8, 26, 29-30, and 45-46 are anticipated by Achen *et al.*

Claims 1-8, 22, 25-27, 29-30, 42, and 45-46 are rejected under 35 U.S.C. 102(e) as being anticipated by Alitalo *et al.* (U.S. Patent No. 6,730,658). Claims 1-3, 5-8, 26 ,29-30, and 45-46 are as stated above. Claims 4, 27, and 42 are drawn to a method of administering VEGF-2 or an effective fragment thereof. Alitalo *et al.* teach administering VEGF-C (also known in the art as VEGF-2, see p. 7 in specification) to patients that are in need of lymphatic tissue growth (column 49, lines 43-49). Alitalo *et al.* teach the use of VEGF-C peptides and effective fragments thereof for the treatment of the physical loss of lymphatic vessels and lymphatic vessel occlusion (see column 5, lines 25-30 and column 9, lines 46-57). Alitalo *et al.* specifically envision treating humans suffering from such endothelial cell disorders (column 9, lines 56-57). Thus, claims 1-8, 26-27, 29-30, 42, and 45-46 are anticipated by Alitalo *et al.*

Claims 1-6, 9, 29-30, and 42-43 are rejected under 35 U.S.C. 102(a) as being anticipated by Eicher (WO 99/49882). Claims 1-6, 29-30, and 42 are as stated above. Claims 9 and 43 are drawn to methods of administering VEGF-2 with at least one angiogenic protein. Eicher teaches the administration of VEGF and VEGF-c to promote new blood and lymphatic vessel formation (see p. 4). Eicher teaches that VEGF and VEGF-C act synergistically (see p. 3). Thus, claims 1-6, 9, 29-30, and 42-43 are anticipated by Eicher.

Claims 1-8, 22, 25-27, 29-30, 42, and 45-46 are rejected under 35 U.S.C. 102(a) and 102(e) as being anticipated by Hu *et al.* (U.S. Patent No. 6,040,157, submitted by Applicants January 27, 2003). Claims 1-8, 22, 25-27, 29-30, 42, and 45-46 are as stated above. Hu *et al.* teach methods of administering VEGF-2 polypeptides or biologically effective fragments thereof for treating the loss of lymphatic vessels, occlusions of lymphatic vessels, and lymphangiomas (see column 30, lines 16-20 and column 38, lines 33-36). Hu *et al.* teach VEGF-2 may be used to treat primary lymphedemas, such as Milroy's disease and Lymphedema precox, and secondary lymphedemas (see column 38, line 56 through column 39, line 7). Thus, claims 1-8, 22, 25-27, 29-30, 42, and 45-46 are anticipated by Hu *et al.*

Conclusion

NO CLAIMS ARE ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Rachel B. Kapust whose telephone number is (571) 272-0886. The examiner can normally be reached on Mon-Fri 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on (571) 272-0887. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

RBK
5/14/04